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Laser Welding With Albumin-Based Solder: Experimental Full-Tubed Skin Graft Urethroplasty

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Background and Objective: **Fistula and stricture formation at the site of sutured anastomoses are frequent complications of major urethroplasty. We performed urethroplasty using laser-welded skin tube grafts in the hope that in addition to being free of suture holes, grafts would be as strong as or stronger than sutured controls.**
Study Design/Material and Methods: **Scrotal skin was harvested from each of 11 rabbits and fashioned into tubes 3–4 cm in length using either conventional suture techniques or laser welding. Welding was performed using an 808-nm diode laser and a dye-enhanced solder composed of albumin and sodium hyaluronate. Laser power density was 15.9 watts/cm^2. For each graft, leak pressure, and urethroplasty time (tube creation and anastomosis to native urethra) were measured.**
Results: **Urethroplasty time was significantly shorter and initial leak pressures were seven times greater in the laser-welded group.**
Conclusions: **The near-uniform occurrence of strictures in both groups suggests that the rabbit is not an ideal model for free tube graft urethroplasty. However, our data indicate that laser welding with albumin-based solder, when used in the appropriate setting, may offer the potential for the rapid creation of watertight grafts in reconstructive urology.**

Key words: glue, reconstruction, urology

INTRODUCTION

Laser welding has been under study in our laboratory for several years. Our technique for tissue welding utilizes an 808-nm diode laser and a protein-based, laser-activated solder. In most studies, fibrinogen-rich protein solders derived from single donor or pooled human plasma have been used [1–5]. In light of the small risk of transmission of bloodborne infections such as hepatitis and human immunodeficiency virus (HIV), recent efforts have focused on human albumin-based solders [6–9]. Albumin, which can be pasteurized [10], provides weld strength indistinguishable from that of cryoprecipitate [11] and thus was selected for this study.

We explored the application of our albumin-based laser solder by performing full-tubed skin graft urethroplasty for anterior urethral replacement in a rabbit model. We hypothesized that laser-welded repairs, in view of the absence of suture holes and gaps between sutures, would be more watertight than sutured controls and might therefore have a reduced incidence of urethrocutaneous fistulae. Laser-welded repairs were compared with conventional microsutured controls in terms of immediate leakage pressure, time of re-

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pair, and clinical course for up to 21 days following urethral surgery.

MATERIALS AND METHODS

Protein Solder Preparation

To 10 ml of a 25% human albumin solution (New York Blood Center, Melville Biologics Division, New York), 1.25 g of human albumin fraction V powder (Sigma, St. Louis, MO) was added to make a 37.5% albumin solution. To remove potential bacterial contamination, sterile filtration through a 0.2 μm pore-size filter was performed. Following filtration, the solution was mixed with sodium hyaluronate (Healon, 10 mg/ml, Kabi Pharmacia Ophthalmics, Monrovia, CA) and indocyanine green (Cardio-Green, 2.5 mg/ml, Becton-Dickinson, Cockeysville, MD) using a sterile technique. Pasteurization to remove potential viral contamination of the human albumin fraction V powder was not perfomed in this experimental glue. Final concentrations were: albumin, 160 mg/ml, sodium hyaluronate, 4.2 mg/ml, and indocyanine green, 0.42 mg/ml.

Laser System

Laser treatments were performed with a diode laser module (Diomed Limited, Cambridge, UK) coupled to a quartz silica fiberoptic (600-μm core diameter). The laser system consists of a phased array of gallium-aluminum-arsenide semiconductor diodes, and the major wavelength output of the diode laser is 808 ± 1 nm. Additional bands of laser energy occur in the visible red spectrum and allow the operator to visualize the spot size of the laser during activation. The spot diameter was ~2 mm at a distance of ~0.5 cm. Laser power was measured at the output of the fiberoptic with a built-in laser power meter in the laser module. The maximum diode power output is 25 W. The laser was used in repeat-pulse mode with the following parameters: power = 0.5 W, pulse duration = 0.5 sec, and pulse interval = 0.1 sec. The power density was 15.9 W/cm^2 and fluence was 8.0 J/cm^2 per pulse.

Laser Welding Technique

We have found that optimal tensile strength and higher bursting pressures can be obtained by following particular guidelines for welding. In general, surfaces to be apposed were freed of clot or active bleeding. Stay sutures were placed to align tissue edges, which in many cases were removed as welding proceeded, providing a truly sutureless tissue closure. A thin "priming" layer of glue was applied between the tissue gap. We have found this step to be essential since thick application of the glue may allow for the top aspect of the glue to heat and dry while the more important underlayer remains in liquid form. The glue was laser activated until blanching followed by glue desiccation occurred.

Operative Technique

The experiment was approved by the Institutional Animal Care and Use Committee of Columbia University. Urethroplasty was performed on 11 New Zealand white male rabbits weighing an average of 3.7 kg (range 3.3–4.0 kg). Optical magnification to 2.5 × was used. All surgery was performed by one of us (A.J.K). All animals were anesthetized with intramuscular ketamine hydrochloride (35 mg/kg) and intramuscular xylazine (5 mg/kg). The abdomen and groin were shaved. Animals were intubated and surgical plane anesthesia was maintained with 2.0% halothane. A cephalosporin was given to all animals preoperatively and maintained for up to 7 days postoperatively.

A sterile towel was sewn just anterior to the anus prior to sterile prep and draping. An 8 Fr pediatric feeding tube was placed per urethra into the bladder and anchored to the glans with silk suture. The phallus was placed on traction by clamping the feeding tube to the abdominal wall. A 2.5 cm incision was made along the ventral aspect of the penis from the midshaft to ~1 cm from the anus. The skin and underlying fascia were undermined creating skin flaps, which were then retracted laterally. An anterior urethrectomy was performed. Hemostasis was achieved with compression and electrocautery.

All animals were subjected to interscrotal skin harvest. The free skin graft was 3.0–4.0 × 0.75–1.0 cm in dimension and was tubularized, epithelial aspect facing intraluminally, over an 8 Fr feeding tube by either laser welding (n = 6) or conventional microsurgical closure (n = 5) with 7-zero polydioxanone suture. Intraluminal pressures were monitored (Datascope, Paramus, NJ) while methylene blue in saline was infused into the tube (prior to anastomosis to the urethra). Leak pressure was determined at the point where saline extravasation was observed.

The feeding tube was then placed intravesically, guiding the tube graft into juxtaposition with the proximal native urethra. In each animal, the same method used to create the tube was used

for anastomosis to the proximal urethra. In the case of laser-welded tubes, 3–4 sutures were used to align the tissue edges, whereas sutured tube anastomoses were performed with continuous suturing. For each graft, times of tube creation and anastomosis to native urethra were measured. The skin and underlying fascia were closed in a continuous fashion with 6-zero polyglactin suture. The urethral stent was cut at the level of the glans and left in place for up to 7 days. A compressive dressing was placed for 24 hours.

Nine additional free scrotal skin grafts were harvested. These were transected and repaired by laser welding to determine tensile strength. Each section was tested using a T10 tensometer (Monsanto, Akron, OH) with crosshead speed of 20 mm/min. The skin was strained perpendicularly to the axis of the closure until ultimate breakage, and tensile break values were recorded.

Animals were sacrificed at 7 (n = 3), 14 (n = 3), and 21 (n = 5) days. Retrograde urethrograms were performed in all animals at the time of sacrifice. Additionally, freshly obtained urethral graft specimens were preserved in 10% formaldehyde solution buffered to physiologic pH for histologic staining with hematoxylin and eosin. Data for operative time and leak pressure were compared by unpaired t-tests. All data are expressed as average ± SD.

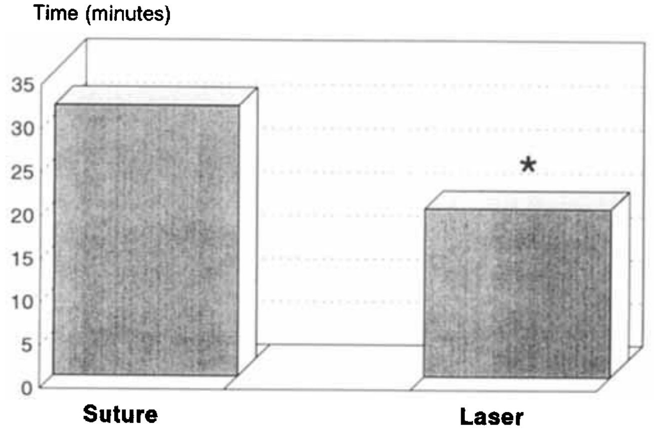

Fig. 1. Comparison of average urethroplasty time for sutured and laser-welded tube grafts. *$P < 0.003$.

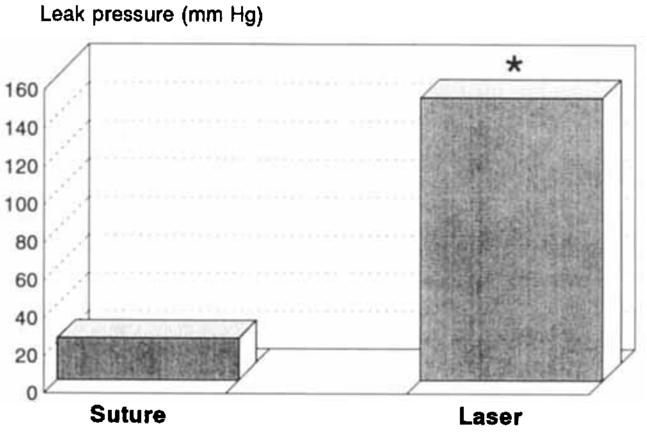

Fig. 2. Comparison of average leak pressure immediately following skin tube construction. *$P < 0.02$.

RESULTS

Eleven full tubed scrotal skin graft urethral reconstructions were performed. Figure 1 illustrates the intraoperative data for urethroplasty time. Time for tube construction and anastomosis to the native urethra was significantly ($P < 0.003$) decreased in the laser-welded group (19.5 ± 2.5 minutes) compared to controls (31.2 ± 3.3 minutes). As shown in Figure 2, immediate leak pressure for laser-welded grafts was 149.2 ± 82.9 mm Hg, and was significantly ($P < 0.02$) higher than that obtained for sutured grafts (22.3 ± 9.4 mm Hg).

The immediate tensile strength for nine laser-welded scrotal skin anastomoses were determined. Samples obtained for this purpose were noted to break at an average of 1.70 ± 0.39 kgF/cm^2. A direct comparison to sutured closures was not performed since this would merely reflect the tensile strength of the sutures. Therefore, as a reference the tensile strength of a 7-zero polydioxanone suture was found to be 0.57 ± 0.04 kg [12].

Radiographic analysis revealed varying degrees of urethral stricture in both the control and laser-welded groups. In the control group, urethral stricture was seen in four animals and fistula without stricture in one. In the laser-welded group, urethral stricture, particularly at the proximal anastomosis, was found in five animals and fistula in none of six animals. No attempt was made to compare the degree of urethral narrowing between groups.

After urethral stents were removed, animals in both groups (3 control, 2 laser welded) were noted to have obstructive voiding signs characterized by dribbling urine and bladder distention. By 21 days, the remaining animals also showed similar signs of obstruction. Microscopic examination at this time revealed extensive squamous keratinization and hyperplasia and extensive periurethral fibrosis (Fig. 3). Although found in a minority, a representative patent laser-welded skin

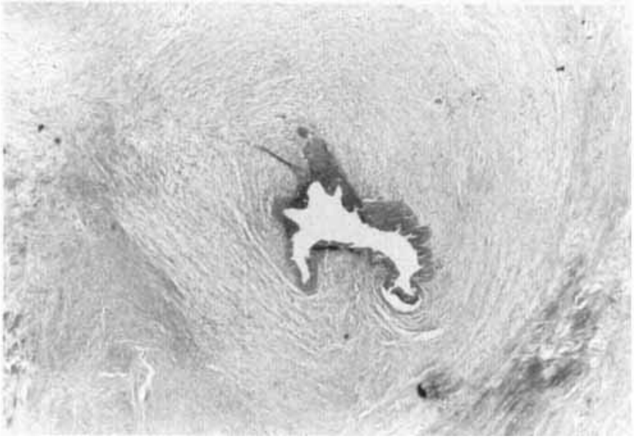

Fig. 3. Stratified squamous epithelium in laser-welded neourethra at 3 weeks. The narrowed lumen is surrounded by keratinized epithelium and a dense fibroplastic reaction. H & E, reduced from × 160.

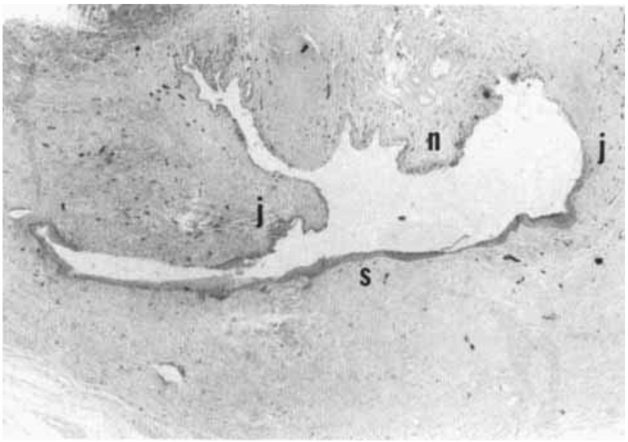

Fig. 4. Microscopic examination of operative site at 3 weeks in a laser-welded repair. The junction (j) of native urothelium (n) and skin graft epithelium (s) at the proximal anatomosis is patent and viable. H & E, reduced from × 160.

tube graft at the proximal anastomosis is illustrated in Figure 4.

DISCUSSION

Enthusiasm for tissue welding stems from the expectation that by providing a watertight seal, laser welding can be a safe—and perhaps superior—alternative to conventional sutured repairs. Urethroplasty studies by others employing free grafts or pedicled grafts [13–15] have provided encouraging results for the application of laser welding to urologic reconstruction. The data presented here indicate that urethroplasty can be performed faster by laser soldering (Fig. 1) and that these welds can withstand seven times the leakage pressure of their sutured counterparts (Fig. 2) while providing excellent tensile strength. Whether this lends itself to a decreased rate of fistula formation could not be ascertained due to the overriding incidence (in both experimental and control groups) of stricture formation. The choice of a solder, the relevance of leakage pressure, and the difficulties inherent in a rabbit model of tube graft urethroplasty all merit further attention.

If laser solders are to substitute for sutures, these solders must be as risk-free as possible. Addition of a chromophore dye lowers the threshold laser energy required for laser welding [16], which serves to minimize collateral thermal damage. However, the laser is not the only source of risk; protein components of laser solders potentially can be contaminated by viruses. A preponderance of earlier studies [1–5] relied on fibrinogen as the principal ingredient in laser solder. Fibrinogen-rich solders were derived from the cryoprecipitate of pooled or single-donor human plasma [17]. Even with current blood-bank protocols, human plasma carries a small risk of transmission of blood-borne pathogens such as hepatitis B (HBV) and HIV. Solvent-detergent treatment [18] can effectively inactivate lipid-coated viruses including HBV and HIV, allowing plasma proteins to remain viable ingredients for laser soldering [19], but solvent-detergent technology currently does not target all blood-borne pathogens, such as the nonenveloped parvovirus B19 [20]. Of note, cryoprecipitate or fibrinogen may be activated chemically by thrombin ("fibrin glue"), circumventing the need for laser activation. Fibrin glue, however, affords little initial strength to a tissue closure [11,21] and still carries the risk of blood-borne pathogens. Previous laser welding studies, alternatively, made use of albumin-based solders, but no direct comparison with fibrinogen or cryoprecipitate was made [6,22]. Recent work in our laboratory [11] indicates that the tensile strength of skin that has been laser-soldered with a human albumin-based preparation is indistinguishable from that of skin laser soldered with cryoprecipitate. Taken together, the risks of cryoprecipitate and the utility of albumin indicate that albumin is a safer solder ingredient for clinical use. It is important to note that our clinical grade solder does not contain fraction V human albumin powder (not available for clinical use). Rather, lyophilization (freeze-

drying) of pasteurized, sterile human albumin (25%) and reconstitution to a concentration of ~40% is performed. Following sterile filtration of this solution, the risks of bacterial and viral contamination are virtually eliminated.

This study addressed the intraoperative performance of an albumin-based laser solder. Free pieces of scrotal skin, when welded together, exhibited a mean breaking strength (per square centimeter) similar to the measured strength of the 7-zero polydioxanone suture. When fashioned into tubes for grafting into urethral defects, laser-welded scrotal skin withstood significantly greater intraluminal pressure than sutured tube grafts. The operative time for laser-welded urethroplasty was significantly shorter than that for conventional sutured urethroplasty. These data confirm claims that laser welding provides a more watertight seal than suturing and that welding can be more easily performed.

The hypothesis that a watertight seal, free from suture holes or gaps, can prevent the development of urethrocutaneous fistulae following urologic surgery could not be adequately addressed in this model. One of five sutured and none of six laser-soldered repairs developed a fistula, an incidence that was not statistically different. The occurrence of strictures, moreover, was noted in four of five sutured and five of six laser-soldered repairs. The near uniform occurrence in both groups suggests that it is a function of the rabbit tube graft model rather than a result of laser-welding versus suturing. Possible reasons include our attempt to graft tubes that, at 3–4 cm in length, were nearly as long as the penile urethra itself; alternatively, the lack of supporting tissue in the rabbit urethra has been suggested as a difficulty common to our and other investigations (Poppas, pers. comm.).

The tissue response to laser soldering has been shown to be invoke less foreign body reaction and decreased inflammation compared to conventional suturing [5,9,13–15,22]. These findings, together with the fact that an immediate seal can be achieved, likely account for the reported success of laser-welded tissue closures.

Although clinical outcome could not be addressed, we found that an albumin-based laser solder gave us rapid, strong, and watertight seals in this model of urethral reconstruction. Modifications are under further study; we have found no complications and 100% graft viability in 14 rabbits subjected to bladder mucosa patch graft urethroplasty using a similar albumin-based solder [9]. In the first eight patients to undergo urinary tract reconstruction using our human albumin-based laser solder, immediate leak pressure was five times higher than suturing alone, and operative time was over two times faster (Kirsch, unpub. data). There have been no complications attributable to laser use in the first 5 months of follow-up. These initial clinical results are encouraging and have been similar to our preclinical experience. These studies provide encouraging support for the continued clinical use of albumin-based laser welding in reconstructive urology.

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